MODERN MEDICINE AND PRACTICE
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EUROPEAN JOURNAL OF MODERN MEDICINE AND PRACTICE
Vol. 4 No. 6 (Jun - 2024) EJMMP ISSN: 2795-921X

CHARACTERISTICS OF IMMUNOLOGICAL CHANGES IN THE DIAGNOSIS OF EARLY RHEUMATOID ARTHRITIS

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Resume: Data from recent years show that active participation of cytokines in the regulation of the autoimmune process in patients with RA has been revealed. An immuno-clinical, i.e., comprehensive examination of patients with clinical stages of rheumatoid arthritis was conducted, in which early rheumatoid arthritis patients had better hand-paw joint arthralgia, shorter duration of morning stiffness, activated B-lymphocytes, IL-2, IL-6, IL-2 than advanced RA. -10, an increase in the blood of TNF-α subpopulations was found to be associated with a low level of CD3, CD4 and rheumatoid factor in the blood.

Keywords: rheumatoid arthritis, V-lymphocytes, cytokine, humoral immunity, interleukin.

According to the WHO, the prevalence of RA in the population is from 0.5% to 1%, in close relatives it reaches 3-5% [1,3,6]. Data from recent years show that active involvement of cytokines in the regulation of the autoimmune process in patients with RA has been identified [2,4]. It was found that cytokines are low-molecular protein molecules (interleukins and growth factors, chemokines, tumor necrosis factor, interferons, etc.) that ensure the process of intercellular communication [5,7].

RA accounts for 10% of the total number of rheumatic diseases, and the annual frequency of new cases is about 0.02%. [5,8,11]. According to prospective studies, the life expectancy of patients with RA is reduced due to organ damage, the development of which is associated with both the development of the immuno-inflammatory process and iatrogenic immunosuppression. It was found that about 70% of erosive-destructive changes in the joints develop within the first 3-6 months from the onset of the disease, which determines an unfavorable prognosis for its course[9,10].

We determined serum levels of IL-1β, IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ in 125 eRA patients, 25 advanced RA patients, and 30 controls (Table 1). Significantly higher levels of IL-2, IL-6, TNF-α and IL-10 in the serum of patients with eRA compared to a group of healthy individuals. The content of IL-2 was three times higher than normal values and averaged 20.50 ± 2.80 pg/ml ($p< 0.05$). IL-6 content was 2.5 times higher than the control group and averaged 32.3 ± 2.6 pg/ml ($p< 0.05$). The content of TNF-α was five times higher than the concentration in the control group and was 40.06 ± 9.56 pg/ml and 7.7 ± 3.98 pg/ml, respectively ($p<0.01$). In patients with ERA, the amount of IL-10 was three times higher than normal (19.30 ± 2.79 pg/ml and 6.23 ± 2.98 pg/ml, respectively; $p< 0.05$).

Table 1 Compared with patients with rheumatoid arthritis and controls, serum cytokine levels in patients with early rheumatoid arthritis

Cytokine pg / ml	Control group (n=30)	eRA (n=125)	RA (n=25)	Reliability of difference (p)	
				P l-2	P 2-3
IL-1b	25.45 ± 5.67	34.06±20.05	57.84±7.74	ND	ND
IL-2	5.92±3.44	20.50±2.80	22.90±10.79	*	*
IL-4	26.48±13.34	39.56±30.68	46.02±2.67	ND	ND
IL-6	13.89±14.56	32.31±2.67	48.32±5.67	*	*
IL-10	6.23 ± 2.98	19.30±2.79	12.81±0.91	*	*
TNF-a	7.72±3.98	40.06±9.56	57.84±7.74	**	ND
γ-IFN	35.34±12.56	71.64±42.69	15.07±6.81	ND	ND

Note: — p<0.05; — p<0.01; ND - differences are not statistically significant

It should be noted that an increase in the level of γ-IFN was detected in patients with eRA compared to normal values (71.64±42.69 pg/ml and 35.34±12.56 pg/ml, respectively), but there were no statistically significant differences.

In the comparative analysis of IL-1β levels in eRA patients and control subjects, there was a tendency to increase in eRA patients (34.06±0.05 pg/ml and 25.45±5.67 pg/ml, respectively), but without reliable differences it didn't happen. We did not observe reliable differences in IL-4 levels in eRA patients compared to controls.

Meanwhile, blood TNF-α levels were significantly increased in eRA patients. It is known that TNF-α is an important inducer of hypersecretion of other anti-inflammatory cytokines, and cytokines play an important role in the initiation and maintenance of immuno-inflammation in RA-affected joints (Suchkov SV et al., 2004; Baugh J. A. et al., 2001) . The importance of TNF-α in the pathogenesis of RA is also confirmed by the fact that suppression of its activity by infliximab (remicade) leads to a decrease in clinical and laboratory activity or remission of the disease (Ziolkowska M. i soavt., 2003).

It should be noted that in patients with RA, there was a statistically significant increase in IL-2 compared to its values in the control group. This chemokine, as you know, is produced by the Th1 type and stimulates the proliferation of V lymphocytes and, accordingly, the production of antibodies. These data justify early therapy in patients with eRA using high-dose GKS and cytostatics to reduce the production of antibodies and AIKs, which provide cytotoxic activity against the articular cartilage and subchondral bone, as well as initiate systemic damage.

A characteristic feature of the cytokine profile in patients with ERA showed an increase in IL-6 levels compared to control values. It is known that IL-6 directly stimulates the synthesis of acute phase proteins by hepatocytes, and together with IL-2, participates in regulating the differentiation of B-cells into plasma cells and stimulates their production of antibodies.

Another important inducer of the inflammatory process is IL-1β, which together with TNF-α is produced mainly by synovial macrophages, stimulates the proliferation of fibroblasts, increases the level of TsOG-2, prostaglandin E2, Th2-lymphocytes, and especially IL-6, under its influence systemic lesions develop (thrombocytosis, hypergammaglobulinemia). Patients with ERA have a tendency to increase IL-1β, which is a natural feature in the current inflammatory environment. It should be assumed that the lack of reliable differences in the level of this pro-inflammatory cytokine in patients with eRA and in the control group may be due to the fact that this cytokine is slightly delayed in the pathological process compared to TNF-α.

It is known that immune T-cell communication in RA patients can be induced by Th1-produced γ-FNO, which has antiviral and immunomodulatory activity. Many researchers point to its ability to initiate T-lymphocyte differentiation, activate macrophages, and reduce the production of the Th2 type. It was observed that the level of γ-IFN increased in the examined eRA patients compared to individuals in the control group, which indicates that it plays an important role in the regulation of cellular cooperation in the context of the development of the immune response associated with the development of the immuno-inflammatory process. It should be noted that a characteristic feature of the cytokine spectrum of patients with eRA is a threefold increase in IL-10 values compared to the values in donors, which indicates the high activity of this anti-inflammatory cytokine at the onset of the disease. IL-4 values tended to increase, but did not differ significantly from values in donors. Our data show that the increase in the amount of anti-inflammatory cytokines (IL-6, TNF-α) at the onset of RA is accompanied by a compensatory increase in the level of the anti-inflammatory cytokine IL-10, which explains the absence of a significant imbalance between the activity of Th1 and Th2 cells at the stage of the formation of the disease.

When studying the cytokine levels in the group of patients with ERA and advanced RA, patients with RA with a short history of the disease had IL-10 (19.30±2.79 pg/ml and 12.81±0.91 pg/ml, respectively; $p< 0.05$) values were found to be high. No reliable differences were obtained in the levels of other cytokines in patients with ERA and advanced RA.

Summary. An immuno-clinical, i.e., comprehensive examination of patients with clinical stages of rheumatoid arthritis was conducted, in which early rheumatoid arthritis patients had better hand-paw joint arthralgia, shorter duration of morning stiffness, activated B-lymphocytes, IL-2, IL-6, IL-2 than advanced RA. -10, an increase in the blood of TNF-α subpopulations was found to be associated with a low level of CD3, CD4 and rheumatoid factor in the blood.

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